JC17 Rec'd PCT/PTO 09 JUL 2001

FORM PTO-1390 (REV 10-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 01398/HG

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/869949

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP00/00095	12 January 2000	12 January 1999

TITLE OF INVENTION: THERAPEUTIC AGENTS FOR CORNEAL DISORDERS

APPLICANT(S) FOR DO/EO/US: Teruo NISHIDA; Katsuhiko NAKATA; and Masatsugu NAKAMURA

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [ ] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment. to remove multiple dependent claims
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [XX] Other items or information: Copy of:
    (i) WO 00/41729, title page only, publication of PCT/JP00/00095
    (ii) English language Int. Search Report Form PCT/ISA/210 (2 pages)
    (iii) English language Int. Prel. Exam. Report, Form PCT/IPEA/409 (4 pages)
    (iv) NOTICE Form PCT/IB/308

Express Mail Mailing Label No.: EL 797 383 154 US

Date of Deposit: July 9, 2001

I hereby certify that this paper and any papers identified herein is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231

Lori Valdes

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09/869949 | PCT/JP00/00095 | ATTORNEY'S DOCKET NUMBER 01398/HG

17. [X] The following fees are submitted:

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BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):	CALCULATIONS PTO USE ONLY
Search Report has been prepared by the EPO or JPO $860.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) $690.00	
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $750.00	
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $1.000.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) $100.00	

ENTER APPROPRIATE BASIC FEE AMOUNT =				$ 860.00	
Surcharge of $130.00 for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$	
CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE	
Total claims	13	- 20 =	0	x 18.00	$ --
Independent claims	3	- 3 =	0	x 80.00	$ --
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+ 270.00	$ --
TOTAL OF ABOVE CALCULATIONS =					$ 860.00
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).					$
SUBTOTAL =					$ 860.00
Processing fee of $130.00 for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).					$
TOTAL NATIONAL FEE =					$ 860.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +					$
TOTAL FEES ENCLOSED =					$ 860.00
				Amount to be: refunded	$
				charged	$

a. [X] A check in the amount of $ 860.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-1378. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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01933
PATENT TRADEMARK OFFICE

Date: July 9, 2001

SIGNATURE

Herbert Goodman
NAME

17,081
REGISTRATION NUMBER

Attorney Docket No. 01398/HG

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Teruo NISHIDA et al

Serial No. : U.S. National Phase Appln. Based on Int. Appln. No. PCT/JP00/00095

Filed : Concomitantly herewith

For : THERAPEUTIC AGENTS FOR CORNEAL DISORDERS

PRELIMINARY AMENDMENT FILED CONCOMITANT WITH APPLICATION

Assistant Commissioner for Patents
Washington, D.C. 20231

S I R :

Please amend the claims as follows:

1. (Amended) A therapeutic agent composition for a corneal disorder comprising a compound having an effect of activating Rho as an active ingredient and a pharmacological carrier.

2. (Amended) The therapeutic agent composition for the corneal disorder as claimed in claim 1, wherein the compound having the effect of activating Rho is lysophosphatidic acid or an acyl derivative thereof.

3. (Amended) The therapeutic agent composition for the corneal disorder as claimed in claim 2, wherein said compound

having the effect of activating Rho is oleoyl lysophosphatidic acid.

4. (Amended) The therapeutic agent composition for the corneal disorder as claimed in claim 1, wherein the corneal disorder is corneal ulcer, corneal erosion, keratitis or dry eye.

5. (Amended) A corneal epithelial migration promoter composition comprising a compound having an effect of activating Rho as an active ingredient and a pharmacological carrier.

Please add the following new claims 6-13:

6. (New) The therapeutic agent composition for the corneal disorder as claimed in claim 2, wherein the corneal disorder is corneal ulcer, corneal erosion, keratitis or dry eye.

7. (New) The therapeutic agent composition for the corneal disorder as claimed in claim 3, wherein the corneal disorder is corneal ulcer, corneal erosion, keratitis or dry eye.

8. (New) A method of treating a corneal disorder comprising administering to a patient in need thereof a therapeutically effective amount of a compound having an effect of activating Rho.

9. (New) The method as claimed in claim 8, wherein the compound having the effect of activating Rho is lysophosphatidic acid or an acyl derivative thereof, wherein said acyl is a saturated or unsaturated higher aliphatic carbonyl or aromatic carbonyl.

10. (New) The method as claimed in claim 9, wherein said compound having the effect of activating Rho is oleoyl lysophosphatidic acid.

11. (New) The method as claimed in claim 8, wherein the corneal disorder is corneal ulcer, corneal erosion, keratitis or dry eye.

12. (New) The method as claimed in claim 9, wherein the corneal disorder is corneal ulcer, corneal erosion, keratitis or dry eye.

13. (New) The method as claimed in claim 10, wherein the corneal disorder is corneal ulcer, corneal erosion, keratitis or dry eye.

REMARKS

It is respectfully submitted that the amended claims and the new claims are supported by the original disclosure and

particularly the disclosure relating to therapeutic compositions starting on page 6 and to the methods of administering therapeutic compositions disclosed on page 7 and further supported by the exemplification on pages 8-12.

The amended claims and the new claims do not include any multiple dependent claims.

The amendments to original claims 1-5 are handmarked on the enclosed copy of these original claims.

Respectfully submitted,

HERBERT GOODMAN
Reg. No. 17,081

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HG/lpv
Enc.: Handmarked copy of original claims 1-5

Claims

1. A therapeutic agent for a corneal disorder comprising a compound having an effect of activating Rho as an active ingredient.

2. The therapeutic agent for the corneal disorder as claimed in claim 1, wherein the compound having the effect of activating Rho is lysophosphatidic acid or an acyl derivative thereof.

3. The therapeutic agent for the corneal disorder as claimed in claim 2, wherein the acyl derivative of lysophosphatidic acid is oleoyl lysophosphatidic acid.

4. The therapeutic agent for the corneal disorder as claimed in any one of claims 1 to 3, wherein the corneal disorder is corneal ulcer, corneal erosion, keratitis or dry eye.

5. A corneal epithelial migration promoter comprising a compound having an effect of activating Rho as an active ingredient.

Specification

Therapeutic Agents for Corneal Disorders

Technical Field

The present invention relates to therapeutic agents for corneal disorders having effects of promoting corneal epithelial migration and containing as active ingredients compounds having effects of activating Rho such as lysophosphatidic acid and acyl derivatives thereof.

Background Art

Corneas are a transparent and avascular tissue having a diameter of about 1 cm and thickness of about 1 mm. Transparency of the cornea affects a visual function greatly. Various physiological and biochemical phenomena in the cornea function mainly for the purpose of maintaining the transparency of the cornea.

Corneal epithelial defect caused by various diseases such as corneal ulcer, corneal erosion, keratitis and dry eye is repaired naturally, unless a mixed infection coincides. However, when the repair is delayed for some reasons or the corneal epithelial defect is persisted without repair, such a delay or persistency exerts harmful influences on normal growth of the epithelium, and further constructions and functions of corneal stroma and endothelium are impaired. A conventional method of treating the corneal epithelial defect is based on a passive principle that corneal epithelium migrates naturally to re-cover defect sites by protecting the corneal surface

from external stimulation. In recent years, with development of cell biology, a factor which participates in division, migration, adhesion, extension and the like of cells has been elucidated. It is reported that a compound which promotes the migration of corneal epithelium plays an important role in repairing the corneal epithelial defect (Clin. Ophthalm., 46, 738-743 (1992), Jpn. J. Ophthalm. Surg., 5, 719-727 (1992)).

Cells respond to outside signals and change a cytoskeleton and a cell adhesion mechanism greatly to adapt them to an outside environment. Main constituents forming the cytoskeleton have three types of fiber structure: a microfilament made of actin and the like, a microtubule made of tubulin and the like and an intermediate filament made of keratin and the like. These constituents perform higher-order functions such as cell adhesion, cell shape, cytokinesis and formation of cell polarity while relating closely each other.

Among them, an Rho family, which is one of subfamilies of low-molecular weight GTP-binding protein, is considered to control the actin-microfilament cytoskeleton. The Rho family consists of members such as Rho, Rac and Cdc 42 and acts downstream from extracellular signals such as cell growth factors. Recently, a target protein which is specific for Rho was identified, and regulation mechanisms of cell phenomena are going to be clarified such as a regulation mechanism of the cytoskeleton and the adhesion (Experimental Medicine, 16, 1782-1788 (1998)) and a regulation mechanism of cell movement (Experimental Medicine, 16, 2032-2039 (1998)).

On the other hand, lysophosphatidic acid and acyl derivatives thereof are known as compounds which activate Rho specifically (Cell, 70, 389-399 (1992)). Various actions were reported with regard to lysophosphatidic acid

and the acyl derivatives thereof. For example, they enhance binding of fibronectin to cells and regulate cell shape (J. Cell Biol., 127, 1447-1459 (1994)). They enhance fibronectin binding to epithelial and endothelial cells in a skin wound (U.S. Pat. No. 5,480,877). They are skin activators with glycosaminoglycan production-accelerating effects, and are useful as cosmetics and external preparations to prevent skin aging (WO 95/35090). They inhibit hyperproliferation of epithelial cells resulting from psoriasis or the like (U.S. Pat. No. 5,565,439). They activate macrophages and inhibit necrosis in tumor cells (U.S. Pat. No. 5,149,527). They inhibit apoptosis and maintain or restore cell functions (WO 98/41213), etc.

In an ophthalmological field, it was reported that lysophosphatidic acid stimulates proliferation of retinal pigment epithelial cells (Curr. Eye Res., 16, 698-702 (1997)), lysophosphatidic acid sensitizes Ca ion influx in cultured lens epithelial cells (Cell. Signal., 9, 609-616 (1997)), corneal injury results in increased production of lysophosphatidic acid and acyl derivatives thereof in aqueous humor, and they promote proliferation of normal keratocytes (Am. J. Physiol., 274, C1065-C1074 (1988)), and the like.

However, there has been no report concerning a relation between Rho and corneal epithelial cells, and it has not been known, of course, whether compounds having effects of activating Rho exhibit effects on a migration mechanism of the corneal epithelium, which is closely related to the repair of the corneal epithelial defect.

As mentioned above, it was a very interesting subject to study effects of the compounds having the effects of activating Rho, which is a low-molecular weight GTP-binding protein participating in the regulation

mechanisms of the cell phenomena, on corneal disorders, particularly on the corneal epithelial migration through studies of participation of Rho in the migration mechanism of the corneal epithelium.

In order to study the participation of Rho in the migration mechanism of the corneal epithelium, the present inventors first studied effects of Rho inhibitors on the corneal epithelium. As a result, it was clarified that the corneal epithelial migration is completely inhibited by the Rho inhibitors and regulation of intracellular scafford protein by Rho, which is the low-molecular weight GTP-binding protein, participates in the migration mechanism of the corneal epithelium.

Next, studying effects of the compounds having the Rho-activating effects, the present inventors found that the compounds have excellent effects of promoting the corneal epithelial migration.

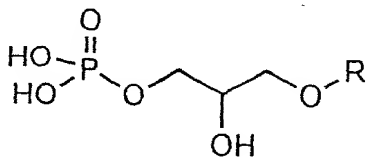
Further, when the compounds having the Rho-activating effects and the Rho inhibitors were used jointly, the above-mentioned promotion of the corneal epithelial migration was almost completely inhibited. It was confirmed that the effects of promoting the corneal epithelial migration are based on the Rho-activating effects.

The above-mentioned results clearly show that the compounds having the Rho-activating effects have the excellent effects of promoting the corneal epithelial migration and are useful as therapeutic agents for corneal disorders such as corneal ulcer, corneal erosion, keratitis and dry eye wherein the cornea is injured from various causes.

Disclosure of the Invention

Compounds having Rho-activating effects in the present invention mean compounds which augment regulation mechanisms of cell phenomena in which Rho participates.

Lysophosphatidic acid and acyl derivatives thereof are compounds represented by the following general formula [I]:



[I]

wherein R is hydrogen or acyl.

The acyl in the compounds [I] is saturated or unsaturated aliphatic carbonyl or aromatic carbonyl, preferably saturated or unsaturated aliphatic carbonyl, more preferably higher aliphatic carbonyl having six or more carbon atoms, and particularly preferred examples of the acyl are oleoyl and stearoyl.

Corneal disorders in the present invention are corneal ulcer, corneal erosion, keratitis, dry eye and the like wherein cornea is injured from various causes.

In order to study participation of Rho in a migration mechanism of corneal epithelium, the present inventors studied the effects of Rho inhibitors and the compounds having the Rho-activating effects, on the corneal epithelium. Details are described in a section of "Pharmacological Tests" hereinbelow. Corneal epithelial migration was recognized to be almost completely inhibited by a C3 enzyme, which is an exoenzyme of *Clostridium botulinum* and is known as the Rho inhibitor (hereinafter referred to as

"Exoenzyme C3") (Cell, 70, 389-399 (1992)).

This result clearly shows that Rho, which is low-molecular weight GTP-binding protein, participates in the migration mechanism of the corneal epithelium.

Next, studying effects of lysophosphatidic acid and the acyl derivatives thereof, which are typical compounds having the Rho-activating effects, on corneal epithelial migration, it was found that lysophosphatidic acid and the acyl derivatives thereof promote corneal epithelial migration in a corneal piece tissue culture system. Further, it was recognized that such corneal epithelial migration-promoting effects are almost completely inhibited by Exoenzyme C3, and it was confirmed that the corneal epithelial migration-promoting effects of lysophosphatidic acid and the acyl derivatives thereof are based on the Rho-activating effects. These results clearly show that the compounds having the Rho-activating effects have excellent effects of promoting the corneal epithelial migration and are useful for treatment of the corneal disorders, namely corneal ulcer, corneal erosion, keratitis, dry eye and the like wherein the cornea is injured from the various causes.

The compound having the Rho-activating effect can be administered orally or parenterally. Examples of dosage forms are tablets, capsules, granules, powders, injections, eyedrops and the like, and eyedrops are particularly preferable. The compound can be formulated into preparations by general techniques. For example, eyedrops can be prepared by optionally using an isotonic agent such as sodium chloride or concentrated glycerine; a buffer such as sodium phosphate or sodium acetate; a surfactant such as polyoxyethylenesorbitan monooleate, polyoxyl 40 stearate or

polyoxyethylene hydrogenated castor oil; a stabilizer such as sodium citrate or disodium edetate; a preservative such as benzalkonium chloride or paraben; or the like. pH can be in a range acceptable for ophthalmic preparations, and it is preferably in a range of 4 to 8. Eye ointments can be prepared by using a general base such as white vaseline or liquid paraffin. Oral preparations such as tablets, capsules, granules and powders can be prepared by optionally adding a diluent such as lactose, crystalline cellulose, starch or vegetable oil; a lubricant such as magnesium stearate or talc; a binder such as hydroxypropylcellulose or polyvinyl pyrrolidone; a disintegrator such as calcium carboxymethylcellulose or low-substituted hydroxypropylmethylcellulose; a coating agent such as hydroxypropylmethylcellulose, macrogol or silicone resin; a film forming agent such as gelatin film; or the like.

The dosage can be selected suitably depending on symptoms, age, dosage form and the like. In the case of eyedrops, they are instilled once to several times per day with a concentration of 0.0001 to 1% (w/v), preferably 0.001 to 1% (w/v) solution. In the case of oral preparations, the usual daily dosage is 0.1 to 5000 mg, preferably 1 to 1000 mg, which can be given in a single dose or several divided doses.

Examples of formulation and results of pharmacological tests are shown below. These examples do not limit the scope of the invention, but are intended to make the invention more clearly understandable.

Best Mode for Carrying out the Invention

Formulation

Typical examples of formulation using oleoyl lysophosphatidic acid (hereinafter referred to as "oleoyl LPA") as a compound having an Rho-activating effect are shown below.

1. Eyedrops

Eyedrops having the following formulation were prepared by a general method.

Formulation 1 (ophthalmic solution)

In 100 ml	
Oleoyl LPA	1 mg
Sodium chloride	900 mg
Sodium hydroxide	q.s.
Hydrochloric acid	q.s.
Sterile purified water	q.s.

Ophthalmic solutions containing 5 mg, 10 mg, 50 mg, 100 mg, 500 mg and 1000 mg of oleoyl LPA in 100 ml can be prepared by optionally adding a surfactant or a stabilizer by a method similar to Formulation 1.

Formulation 2 (eye ointment)

In 100 g	
Oleoyl LPA	100 mg
White vaseline	90 g
Liquid paraffin	q.s.

Eye ointments containing 1 mg, 5 mg, 10 mg and 50 mg of oleoyl LPA

can be prepared by a method similar to Formulation 2.

Formulation 3 (tablet)

In 100 mg	
Oleoyl LPA	10 mg
Lactose	59.4 mg
Cornstarch	20 mg
Calcium carboxymethylcellulose	6 mg
Hydroxypropylcellulose	4 mg
Magnesium stearate	0.6 mg

Desired coated tablets can be obtained by coating tablets according to the formulation as above with 2 mg/tablet of a coating agent such as hydroxypropylcellulose.

Tablets containing 0.1 mg, 0.5 mg, 1 mg, 5 mg and 50 mg of oleoyl LPA in 100 mg can be obtained by a method similar to Formulation 3.

Pharmacological Tests

Effect on corneal epithelial migration (in vitro)

Effects of the following test compounds on corneal epithelial migration were studied using cornea of a male Japanese white rabbit by using corneal epithelial migration length in a corneal piece tissue culture system as an index according to the method of Nishida et al. (J. Cell Biol., 97, 1653-1657 (1983)).

Experimental method

A corneal block isolated from a corneal piece of a rabbit was cultured for 24 hours in a culture medium (TC-199) containing the test compound under a condition of 37℃-5% CO_2. After the culture, the corneal block was fixed in a mixed liquid of ethanol-glacial acetic acid (volume ratio 95:5) and embedded with paraffin to prepare a section. Removing the paraffin from the section, the section was stained with hematoxylin-eosin, and migration length of an epithelial cell layer was measured under a microscope.

A corneal block cultured similarly in a culture medium containing no test compound was used as a control.

Result 1

Table 1 shows a result obtained by culturing the corneal block in a culture medium containing Exoenzyme C3, which is an Rho inhibitor, as the test compound.

Table 1

	Migration length (μ m)
Control	454
Exoenzyme C3 (2 μ g/ml)	186

(Each datum in the table is an average of six samples.)

Table 1 clearly shows that when the corneal block is cultured in the culture medium containing Exoenzyme C3, which is the Rho inhibitor, the corneal epithelial migration is almost completely inhibited, and Rho participates in the corneal epithelial migration.

Result 2

Table 2 shows results obtained by culturing the corneal block in a

culture medium containing oleoyl LPA as the test compound at concentrations of 0.02 μM, 0.2 μM and 2 μM respectively.

Table 2

	Migration length (μm)
Control	454
Oleoyl LPA (0.02 μM)	528
(0.2 μM)	658
(2 μM)	712

(Each datum in the table is an average of six samples.)

Table 2 shows that when the corneal block is cultured in the culture medium containing oleoyl LPA, the corneal epithelial migration is remarkably promoted concentration-dependently.

Result 3

Table 3 shows results obtained by adding Exoenzyme C3 to the culture medium together with oleoyl LPA as the test compounds.

Table 3

	Migration length (μm)
Control	454
Exoenzyme C3 (2 μg/ml)	
+ Oleoyl LPA (0.02 μM)	185
+ Oleoyl LPA (0.2 μM)	182
+ Oleoyl LPA (2 μM)	198

(Each datum in the table is an average of six samples.)

Table 3 shows that when Exoenzyme C3, which is the Rho inhibitor, is added to the culture medium together with oleoyl LPA, the corneal

epithelial migration is almost completely inhibited.

These results confirm that the corneal epithelial migration-promoting effect is based on the Rho-activating effect.

The above-mentioned pharmacological tests show that the compound having the Rho-activating effect has the excellent effects of promoting corneal epithelial migration and is useful as a therapeutic agent for corneal disorders such as corneal ulcer, corneal erosion, keratitis and dry eye wherein the cornea is injured from various causes, through an effect of promoting wound healing of the corneal epithelium.

Industrial Applicability

The present invention relates to therapeutic agents for corneal disorders containing compounds having Rho-activating effects as active ingredients, for example corneal epithelial migration promoters.

Claims

1. A therapeutic agent for a corneal disorder comprising a compound having an effect of activating Rho as an active ingredient.

2.The therapeutic agent for the corneal disorder as claimed in claim 1, wherein the compound having the effect of activating Rho is lysophosphatidic acid or an acyl derivative thereof.

3. The therapeutic agent for the corneal disorder as claimed in claim 2, wherein the acyl derivative of lysophosphatidic acid is oleoyl lysophosphatidic acid.

4. The therapeutic agent for the corneal disorder as claimed in any one of claims 1 to 3, wherein the corneal disorder is corneal ulcer, corneal erosion, keratitis or dry eye.

5. A corneal epithelial migration promoter comprising a compound having an effect of activating Rho as an active ingredient.

Abstract

The present invention provides therapeutic agents for corneal disorders comprising compounds having effects of activating Rho as active ingredients, for example corneal epithelial migration promoters. The compounds having the effects of activating Rho are exemplified by lysophosphatidic acid and acyl derivatives thereof. The corneal disorders are exemplified by corneal ulcer, corneal erosion, keratitis and dry eye.

10/96FHGL&C

U.S. Attorney Docket _____

APPLICATION FOR UNITED STATES LETTERS PATENT

PCT Declaration and Power of Attorney (35 U.S.C. 371(c)(4))
PCT Application - United States Designated Office

As a below named inventor, I declare that:

My residence, post office address and citizenship are as stated below next to my name; I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Therapeutic Agents for Corneal Disorders

described and claimed in International Application number PCT/JP00/00095 filed 12 January 2000 and, if it was amended, as amended on

I have reviewed and understand the contents of said specification, including claims.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I claim priority benefits under 35 USC §119 of: (i) any foreign application(s) for patent or inventor's certificate listed below; or (ii) any United States provisional application(s) listed below; and have also identified below any foreign application(s) for patent or inventor's certificate, or PCT international application having a filing date before that of the application(s) on which priority is claimed.

COUNTRY	APPLICATION NUMBER	DATE (day, month, year)	PRIORITY CLAIMED
Japan	Pat.11-5420	12 Jan.1999	yes XX no_____
			yes_____ no_____

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I appoint the following attorneys to prosecute this application and to transact all business in the U.S. Patent & Trademark Office connected therewith: Leonard Holtz, Reg. No. ~~22,974;~~ ~~Herbert~~ Goodman, Reg. No. 17,081; Thomas Langer, Reg. No. 27,264; Marshall J. Chick, Reg. No. ~~26,853;~~ Richard S. Barth, Reg. No. 28,180; ~~Douglas~~ Holtz, Reg. No. 33,902; and Robert P. Michal, Reg. No. 35,614.

CORRESPONDENCE AND CALLS TO: FRISHAUF, HOLTZ, GOODMAN, LANGER & CHICK, P.C.
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INVENTOR: SIGNATURE	DATE	RESIDENCE AND POST OFFICE ADDRESS
Sign: Teruo Nishida	Date: July 26, 2001	Residence: (City & Country) Ube-shi, Japan JPX Post Office Address: 396-2, Oaza Nishikiwa, Ube-shi, Yamaguchi 750-0151 Japan
Type: Teruo NISHIDA	Citizen of: Japan	
Sign:	Date:	Residence: (City & Country) Sakurai-shi, Japan JPX Post Office Address: 531-1, Oaza Hashinaka, Sakurai-shi, Nara 633-0072 Japan
Type: Katsuhiko NAKATA	Citizen of: Japan	
Sign:	Date:	Residence: (City & Country) Nara-shi, Japan Post Office Address: 12-3-205, Mimatsu 2-chome, Nara-shi, Nara 631-0074 Japan
Type: Masatsugu NAKAMURA	Citizen of: Japan	

10/96FHGL&C U.S. Attorney Docket _____

APPLICATION FOR UNITED STATES LETTERS PATENT

PCT Declaration and Power of Attorney (35 U.S.C. 371(c)(4))
PCT Application - United States Designated Office

As a below named inventor, I declare that:

My residence, post office address and citizenship are as stated below next to my name; I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Therapeutic Agents for Corneal Disorders

described and claimed in International Application number PCT/JP00/00095 filed 12 January 2000 and, if it was amended, as amended on

I have reviewed and understand the contents of said specification, including claims.
I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I claim priority benefits under 35 USC §119 of: (i) any foreign application(s) for patent or inventor's certificate listed below; or (ii) any United States provisional application(s) listed below; and have also identified below any foreign application(s) for patent or inventor's certificate, or PCT international application having a filing date before that of the application(s) on which priority is claimed.

COUNTRY	APPLICATION NUMBER	DATE (day, month, year)	PRIORITY CLAIMED
Japan	Pat.11-5420	12 Jan.1999	yes XX no_____
			yes_____ no_____

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I appoint the following attorneys to prosecute this application and to transact all business in the U.S. Patent & Trademark Office connected therewith: Leonard Holtz, Reg. No. 22,974; Herbert Goodman, Reg. No. 17,081; Thomas Langer, Reg. No. 27,264; Marshall J. Chick, Reg. No. 26,853; Richard S. Barth,Reg. No. 28,180; Douglas Holtz, Reg. No. 33,902; and Robert P. Michal, Reg. No. 35,614.

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